Distinct Roles of MicroRNA-1 and -499 in Ventricular Specification and Functional Maturation of Human Embryonic Stem Cell-Derived Cardiomyocytes.

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Public Summary:
BACKGROUND: MicroRNAs (miRs) negatively regulate transcription and are important determinants of normal heart development and heart failure pathogenesis. Despite the significant knowledge gained in mouse studies, their functional roles in human (h) heart remain elusive. METHODS AND RESULTS: We hypothesized that miRs that figure prominently in cardiac differentiation are differentially expressed in differentiating, developing, and terminally mature human cardiomyocytes (CMs). As a first step, we mapped the miR profiles of human (h) embryonic stem cells (ESCs), hESC-derived (hE), fetal (hF) and adult (hA) ventricular (V) CMs. 63 miRs were differentially expressed between hESCs and hE-VCMs. Of these, 29, including the miR-302 and -371/372/373 clusters, were associated with pluripotency and uniquely expressed in hESCs. Of the remaining miRs differentially expressed in hE-VCMs, 23 continued to express highly in hF- and hA-VCMs, with miR-1, -133, and -499 displaying the largest fold differences; others such as miR-let-7a, -let-7b, -26b, -125a and -143 were non-cardiac specific. Functionally, LV-miR-499 transduction of hESC-derived cardiovascular progenitors significantly increased the yield of hE-VCMs (to 72% from 48% of control; $p<0.05$) and contractile protein expression without affecting their electrophysiological properties ($p>0.05$). By contrast, LV-miR-1 transduction did not bias the yield ($p>0.05$) but decreased APD and hyperpolarized RMP/MDP in hE-VCMs due to increased I(to), I(Ks) and I(Kr), and decreased I(f) ($p<0.05$) as signs of functional maturation. Also, LV-miR-1 but not -499 augmented the immature Ca(2+) transient amplitude and kinetics. Molecular pathway analyses were performed for further insights. CONCLUSION: We conclude that miR-1 and -499 play differential roles in cardiac differentiation of hESCs in a context-dependent fashion. While miR-499 promotes ventricular specification of hESCs, miR-1 serves to facilitate electrophysiological maturation.

Scientific Abstract:
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